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10/018,875	03/22/2002	Midori Shima	2462-132US	8702

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EXAMINER

SWOPE, SHERIDAN

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 03/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	10/018,875	SHIMA ET AL.
	Examiner	Art Unit
	Sheridan L. Swope	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 02 February 2004.
- 2a) This action is **FINAL**.                  2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 3-19 is/are pending in the application.
- 4a) Of the above claim(s) 3,9 and 14-18 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 4-8, 10-13, and 19 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)             | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____.  | 6) <input type="checkbox"/> Other: _____.                                   |

### **DETAILED ACTION**

Applicant's response, on February 2, 2004 to the First Action on the Merits of this case, mailed August 1, 2003, is acknowledged. It is acknowledged that applicants have cancelled Claims 1 and 2; amended Claims 4, 5, 7, 8, and 10-13, and added new Claims 14-19. Claims 4-8 and 10-19 are pending. Claim 13, as amended, is encompassed by the elected invention. Claims 14-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Claims 4-8 and 10-13 are hereby reconsidered and Claim 19 is considered on their merits.

#### *Specification-Objections*

Objection to the application for poor grammar and sentence construction is maintained. It is acknowledged that Applicants have corrected the errors listed in the prior action. However, said list was only exemplary, not exhaustive. Applicants are expected to correct all grammatical defects in the Application. It is suggested that Applicants make use of a professional scientific translator or scientific editor.

#### *Claims-Objections*

Claim 4 is objected to for lack of clarity and the following grammatical changes are suggested. (i) The phrase "which is capable of inhibiting the reaction of a serine protease with a substrate thereof" should be set off by commas [,]. (ii) On line 4, -the- should be inserted between "substrate of" and "serine protease" i.e. "substrate of [the] serine protease".

Claim 6 is confusing in the recitation of "is made solely of". It is suggested said phrase be replaced with "is solely".

For clarity, a comma [,] should be inserted in Claim 13, line 3, i.e. "inhibitor[,] as"

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claims 4-8, 10-13, and 19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 3-6 of copending Application No. 10/018,251.

Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 4-8, 10-13, and 19 herein and Claims 3-6 of 10/018,251 are both directed to serine protease inhibitors formed by anhydridization of an active serine protease, wherein said

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inhibitor binds to the substrate in competition with the active protease. The claims differ in that Claims 4, 6, 10-13, and 19 herein recite inhibitors of any serine protease, while Claims 3-6 of 10/018,251 specifically recite inhibitors of blood coagulation factors. However, Claim 5 herein recites inhibitors of the blood coagulation factors II, VII, IX and X. The portion of the specification in 10/018,251 that supports the recited inhibitors includes embodiments that would anticipate Claims 4-8 and 10-13 herein, e.g., inhibitors of serine proteases that are blood-coagulating factors and methods of making said inhibitors. Claims 4-8, 10-13, and 19 herein cannot be considered patentably distinct over Claims 3-6 of 10/018,251 when there are specifically recited embodiments (inhibitors of serine proteases that are blood-coagulating factors produced by anhydridization of the active-site serine) that would anticipate Claims 4-8, 10-13, and 19 herein. Alternatively, Claims 4-8, 10-13, and 19 herein cannot be considered patentably distinct over Claims 3-6 of 10/018,251 when there are specifically disclosed embodiments in 10/018,251 that supports Claims 3-6 of that patent and falls within the scope of Claims 4-8 and 10-13 herein; because, it would have been obvious to a skilled artisan to modify the inhibitors of Claims 3-6 of the copending application by selecting a specifically disclosed embodiment that supports these claims, i.e., inhibitors of serine proteases that are blood-coagulating factors produced by anhydridization of the active site serine residue. One having ordinary skill in the art would have been motivated to do this, because that embodiment is disclosed as being a preferred embodiment within Claim 3-6.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Claim Rejections - 35 USC § 112-Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-8, 10-13, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite in the recitation of “A serine protease inhibitor containing an anhydridized serine protease”. It is unclear whether applicants are reciting a composition comprising the anhydridized protease or an anhydridized protease that is an inhibitor.

Clarification is required. Claims 5-8, 10-13, and 19, as dependent from Claim 4, are rejected for the same reasons. For purposes of examination, it is assumed that Claim 4 is meant to recite a serine protease inhibitor, which is an anhydridized serine protease.

Claim 19 is indefinite in the recitation of “dehydroalanine”. It is assumed that applicants mean to recite “dehydroalanine”. However, “dehydroalanine” is also indefinite, as alanine does not contain a hydroxyl group. For purposes of examination, it is assumed that Claim 19 is meant to recite “dehydroserine”, which is alanine.

***Claim Rejections - 35 USC § 112-First Paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of Claims 4, 5, and 10-13 under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained. The detailed reasons for this rejection are presented in the prior action.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments. (i) Claim 5 has been amended to limit the serine protease inhibitor to **activated** blood coagulation factors II, VII, IX, and X [Applicant's emphasis]. (ii) The serine protease inhibitor of the present invention is an inhibitor obtained by substituting dehydroalanine for the active serine residue. (iii) The claimed inhibitor is limited by its functionality, i.e., capable of inhibiting the reaction of a serine protease with a substrate thereof by binding itself to said substrate of serine protease in competition with said serine protease.

These arguments are not found to be persuasive for the following reasons. The specification fails to enable one of skill in the art to make the full scope of the serine protease inhibitors recited in Claims 4 and 5. Claim 4 is so broad as to encompass any inhibitor derived from any serine protease, that is anhydridized on any residue, and that is able to competitively block native protease binding to substrate. Claim 5 is so broad as to encompass any of activated blood coagulation factors II, VII, IX, and X, that is anhydridized on any residue, and that is able to competitively block native factor binding to substrate. The specification does not teach one of skill in the art how to make all said anhydridized proteases. Neither Claim 4 nor Claim 5 recite an inhibitor obtained by substituting dehydroserine/alanine for the active serine residue. It is acknowledged that the claimed inhibitor is limited by its functionality. However, the fraction of inhibitors, encompassed by the scope of Claims 4 and 5, that have the desired biological characteristics is small; and, determining which inhibitors have the desired characteristics

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represents undue experimentation for a skilled artisan. Rejection of Claims 10-13, which recite compositions comprising the inhibitors of Claim 4, is maintained for the same reasons.

Rejection of Claims 4, 5, and 10-13 under 35 U.S.C. 112, first paragraph, for insufficient structural written description is also maintained. Applicants did not comment on said rejection.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior action rejected Claims 1, 2, and 10-13 under 35 U.S.C. 102(b) as being anticipated by Paetzel et al 1997 as evidenced by Tschantz et al, 1993. Because Claims 1 and 2 have been cancelled, said rejection is withdrawn. However based on Applicant's amendment, Claims 4, 10-13, and 19 are now rejected under 35 U.S.C. 102(b) as being anticipated by Paetzel et al 1997, as evidenced by Tschantz et al, 1993.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments. "To be an appropriate basis for a 102 rejection, a *single* cited reference must include each and every element. The compounds of the present invention are obtained by substituting dehydroalanine [alanine] for the active serine residue. In contrast, Paetzel et al teach a modified leader peptidase and make no mention of any competitive inhibition activity of said modified compound. There can be no simple correlation, i.e., "inherency", that shows that different alteration of different peptides on different proteins will have identical biochemical effects. The Paetzel et al reference teaches that the lysine modifier, malaeic anhydride inhibits the

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peptidase by reacting with Lys<sup>145</sup>, ...it does not support the position that this disclosure teaches an anhydridized serine protease or the competitive inhibition of serine protease. The references cited disclose different compounds with different inactivates/activities."

These arguments are not found to be persuasive for the following reasons. The protein taught by the single cited reference of Paetzel et al, includes each and every element of a serine protease inhibitor encompassed by Claim 4. Paetzel et al teach an anhydridized serine protease, which competitively blocks binding of the non- anhydridized serine protease to the substrate. Tschantz et al merely corroborates the characteristics of the protein of Paetzel et al. The compounds of the invention examined herein are not necessarily obtained by substituting dehydroserine/alanine for the active-site serine residue but are anhydridized serine proteases; see the Restriction requirement of March 26, 2003 and Applicant's election of April 28, 2003. Claims 4 and 5 do not recite substituting dehydroserine/alanine for the active-site serine residue or anhydridization of active-site serine residues. It is acknowledged that the effect of mutating or derivatizing proteins on the function of the protein is unpredictable. However, one of skill in the art would conclude that the effect on the enzymatic activity and the ability to bind to substrate of mutating Lys<sup>145</sup> and anhydridizing Lys<sup>145</sup> would be the same. As discussed in the previous action, when the leader peptidase of Paetzel is mutated on Lys<sup>145</sup>, the mutated inactive peptidase acts as a competitive inhibitor of wild-type protease binding to substrate (Tschantz et al). A skilled artisan would conclude that, the anhydridized serine protease of Paetzel et al has the same functional characteristics and, therefore, Paetzel teaches each and every element of a serine protease inhibitor encompassed by Claim 4.

Rejection of Claims 4-8 and 10-13 under 35 U.S.C. 102(b), as being anticipated by Ashton et al, 1995 (in IDS) as evidenced by Arcone et al, 1999, is maintained. New Claim 19 is hereby also rejected under 35 U.S.C. 102(b), as being anticipated by Ashton et al, 1995, as evidenced by Arcone et al, 1999. In support of their request that said rejection be withdrawn, Applicants provide the following arguments. "To be an appropriate basis for a 102 rejection, a *single* cited reference must include each and every element. The cited reference [Ashton et al] does not disclose that it's variant can bind to a serine protease substrate or that it performs as a competitive serine protease inhibitor. In the competitive assay of anhydrothrombin and thrombin, both were found to bind to hirudin in approximately a 1:1 ratio; thus, there is not indication or support for the position that anhydridized serine protease, such as anhydrothrombin is useful as a serine protease inhibitor.

These arguments are not found to be persuasive for the following reasons. The protein taught by the single cited reference of Ashton et al, includes each and every element of a serine protease inhibitor encompassed by Claims 4-6. Ashton et al teach a variant of activated blood coagulating factor II (thrombin) that is anhydridized on the active-site serine residue, Ser<sup>205</sup> (Table 2) and competes with thrombin for binding of substrate. Ashton et al clearly state that, "anhydrothrombin remained bound in a complex with hirudin in the presence of added thrombin, demonstrating effective competition with thrombin for binding to hirudin" (pg 6461, par 10, lines 6-9). It is acknowledged that hirudin is a substrate analogue, not a substrate. However, hirudin binds to the same site on thrombin as the substrate (Stone et al, 1986) and a person of ordinary skill in the art would believe that, because the anhydrothrombin binds hirudin, anhydrothrombin would bind thrombin substrate. Said belief is corroborated by the teachings of

Arcone et al, showing that [Ser<sup>205</sup>Ala]- thrombin is catalytically inactive (Fig 1), competes with wild-type thrombin for binding to the substrate thrombin receptor, and inhibits thrombin-mediated proteolytic activation of the thrombin receptor (Fig 5C). Thus, Ashton et al teach a variant serine protease, anhydrothrombin (Factor II), that is anydridized on the active-site serine residue and acts a competitive inhibitor of thrombin by binding to a thrombin substrate, which is encompassed by Claims 4-6 and 10-13. The anhydridization reaction taught by Ashton et al chemically converts Ser<sup>205</sup> to an alanine residue (Fig 1), which is encompassed by Claim 19.

Rejection under 35 U.S.C. 102(b) of Claims 7 and 8, as being anticipated by Ashton et al, 1995 (in IDS) in view of Arcone et al, 1999, is also maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Rejection of Claims 4-8 and 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paetzel et al 1997 in view of Berkner et al, 1998 and further in view of Ashton et al, 1995, as described in the prior action, is maintained. New Claim 19 is hereby also rejected under 35 U.S.C. 103(a), as being unpatentable over Paetzel et al 1997 in view of Berkner et al, 1998 and further in view of Ashton et al, 1995.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments. (i) None of the references disclose or suggest the compounds of the present invention. Paetzel et al teach a totally different compound and there is no teaching or

suggestion in Paetzel to change a different peptide or to look to Berkner et al or Ashton et al for such modification. (ii) As noted above, Ashton et al discloses a variant that competes with wild-type factor II for binding to a substrate analog; no binding with an actual substrate is disclosed. There is no teaching or suggestion in Ashton et al that the combination would impart competitive-inhibitor characteristics on compounds which it discloses have no such activity. (iii) The only motivation making the complex combination of references suggested in the Action is to study the role of active-site serine in the function of clotting factors. (iv) As noted in the Action, modification of a protein's amino acid(s) that can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited and the results of such modifications are unpredictable.

These arguments are not found to be persuasive for the following reasons. It is acknowledged that, except for anhydrothrombin as discussed above, none of these references disclose the compounds of Claims 4-6, 10-13, and 19; however they are not required to, as this is a rejection under 35 U.S.C. 103(a), not 35 U.S.C. 102. Applicant's argument that Ashton et al only discloses a variant that binds a substrate analog and that Ashton et al do not teach that the variant binds substrate competitively are addressed above. Paetzel et al teach that anhydridization of a protease has utility in determining the active site residue (Fig 5), while Ashton et al clearly state that their "method of preparation of anhydro derivatives may be generally applicable to a variety of serine proteases" (pg 6455, parg 6, lines 9-11). These teachings of Paetzel et al and Ashton et al suggest and provide motivation for the anhydridization of serine proteases. Furthermore, because an anhydridized protease can compete with the native

enzyme for binding substrate, as taught by Ashton et al, a person of ordinary skill in the art would be motivated to make anhydridized proteases to be used as therapeutic agents.

It is acknowledged that the effect of mutating or derivatizing a protein on the function of the protein is unpredictable. However, as discussed in the prior action, the art teaches that anyhydridization of the active-site serine residue of serine proteases is, more likely than not, to produce a protease variant that is catalytically inactive but has binding activity. Anhydridization of thrombin using PMSF produces a thrombin variant that binds a substrate analog (Ashton et al). Said anhydridization of thrombin results in a chemical conversion of the active site serine, Ser<sup>205</sup>, to an alanine (Ashton et al, Fig 1). Conversion of said serine residue to alanine, using recombinant technology, shows that [Ser<sup>205</sup>Ala]-thrombin is catalytically inactive but binds substrate (Arcone et al, 5C). Others have shown that conversion of an active-site serine residue to an alanine residue results in a protease variant that is catalytically inactive but has binding activity (Berkner et al, 1998; Example III and Gale et al, 1997; Table 1 and Fig 3). Thus, it was known in the art that, conversion of an active-site serine residue to alanine, by either chemical or mutagenic means, results in an inactive serine protease that has binding activity. As also discussed in the prior action, the general applicability of anhydridization for the preparation of enzymes without catalytic activity but with binding activity was known in the art. For example, Tschantz et al, 1993 teach a protease that has been anhydridized on a lysine residue; said protease is inactive but competes with the wild-type protease for binding to substrate (Figs 4 & 6). In a second example, Abouakil et al, 1989 teach a lipase that has been anhydridized on the active site histidine residue; said lipase is inactive but still binds to substrate (Figs 2 & 5). Thus, a person of ordinary skill in the art would predict that conversion of the active-site serine residue

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of serine protease by anhydridization would produce a inactive protease variant that has substrate binding activity and functions as a protease inhibitor.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

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Sheridan Lee Swope, Ph.D.

*Rebecca E. Ph.D.*  
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